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PRINCIPAL INVESTIGATOR: Richard F. Seegal, Ph.D.

CONTRACTING ORGANIZATION: Health Research, Incorporated  
Rensselaer, New York 12144

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## INTRODUCTION

The major hypotheses to be tested in this project are that high-level occupational exposure of former capacitor workers to polychlorinated biphenyls (PCBs) will result in reductions in (i) performance on neuropsychological and neurological tests that reflect the historic PCB body burden of the individual; (ii) the number of dopamine (DA) terminals in the basal ganglia that correlate with behavioral change and (iii) circulating levels of thyroid hormones.

Aging former capacitor workers, previously employed at capacitor manufacturing facilities located approximately fifty miles north of Albany, NY, are undergoing neuropsychological and neurological exams, completing a comprehensive occupational, residential and dietary questionnaire, having blood drawn to measure serum thyroid hormone and PCB concentrations, and undergoing a non-invasive test to determine bone lead concentrations in Albany, NY. This latter measure will reduce the likelihood of confounding the neurological effects of prior PCB exposure with the neurological effects of prior lead exposure. Finally, approximately 40% of the subjects are also participating in a second portion of the study that uses brain  $\beta$ -CIT SPECT imaging to determine whether prior occupational exposure to PCBs reduces the number of basal ganglia DA terminals. Imaging takes place at the Institute for Neurodegenerative Disorders in New Haven, CT under the supervision of Dr. Kenneth Marek.

In order to test the above hypotheses we have gathered a team of internationally recognized experts in the epidemiology of environmental and occupational exposure to PCBs, the neurology of movement disorders and Parkinson's Disease, the assessment of toxicant-induced deficits in neuropsychological function, measurement of serum PCB concentrations, non-invasive determination of bone lead concentrations, and brain imaging of central dopamine neurons and their relationship to movement disorders, including Parkinson's Disease.

## STUDY INVESTIGATORS

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### Albany, NY Based Testing

**Richard F. Seegal - Wadsworth Center, New York State Dept. of Health (NYSDOH):**

Principal Investigator

**Edward F. Fitzgerald, Lenore J. Gensburg - Center for Environmental Health, NYSDOH**

Tracing, Screening, Residential, Occupational, Dietary and Medical Histories

**Stewart A. Factor, Eric S. Molho - Albany Medical Center: Neurological Assessment**

**Robert J. McCaffrey - University at Albany: Neuropsychological Assessment**

**Richard F. Haase - University at Albany: Biostatistician**

**Mary S. Wolff - Mount Sinai School of Medicine: Serum PCB Analyses**

**Andrew S. Todd - Mount Sinai School of Medicine: Bone Lead Determination**

**Patrick Parsons - Wadsworth Center, NYSDOH: Bone Lead Determination**

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### New Haven, CT Based Testing

**Kenneth Marek, John P. Seibyl, Danna Jennings - Institute for Neurodegenerative Disorders:  $\beta$ -CIT SPECT Brain Imaging**

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### What has Changed This Year?

#### Personnel

There have been several changes during the last year. Nevertheless, we have been fortunate in finding highly talented individuals to replace those who have left—resulting in neither a loss of time nor a reduction in the number of subjects who have undergone testing.

Dr. Factor will shortly be leaving Albany to become Director of the Movement Disorder Clinic at Emory University. Dr. Donald Higgins, also a Parkinson's disease neurologist at the Parkinson's Disease and Movement Disorders Center of Albany Medical Center, will contribute his expertise to the project (see Appendix 1 for a copy of his curriculum vita).

Dr. Edward Fitzgerald continues to contribute to this project, but has moved from the Center for Environmental Health of the New York State Department to the Department of Epidemiology and Biostatistics of the University of Albany. His change of institutions, but not cities, was motivated by his desire to devote a larger portion of his efforts to research, including this project.

Ms. Gwen Mergian, the Study Coordinator, resigned and has been replaced with Ms. Sue Heckman, who previously carried out the bone lead measurements.

Ms. Lakhana Weaver has been hired (50% effort) to carry out the bone lead measurements previously conducted by Ms. Heckman.

#### We Are Collecting Sera for Analysis of Thyroid Hormone Function

A study of electrical workers at the La Salle Electrical Utilities Company in La Salle Illinois (Final Report to the Agency for Toxic Substances Disease Registry, May 2002) demonstrated altered thyroid hormone function following exposure to PCBs at levels similar to those seen in our subjects. We decided, based on the fact that altered thyroid hormone function may affect some of our measures, to also determine if circulating levels of thyroid hormones are altered in workers in our study.

We received IRB approval to begin collecting an additional tube of blood from each subject (one tube is for analysis of serum PCB concentrations) in order to determine T<sub>3</sub>, T<sub>4</sub> and free TSH levels. We have presently collected an additional blood sample from 48 subjects. We will, in this fiscal year, request modification of the Statement of Work (SOW) and additional monies to carry out the above described analyses.

#### We Have Modified Our Procedures for Selecting Subjects for Inclusion in the Study

Until recently, we randomly selected subjects from computer lists that contain the names and addresses of all individuals who worked for at least three months at either the Ft. Edward or Hudson Falls, NY capacitor plants. However, examination of job description codes for prospective subjects who had not participated in the earlier study by scientists from Mt. Sinai Medical Center (*i.e.*, those with archived sera) demonstrated that approximately 1/3<sup>rd</sup> of the subjects did not have any jobs that involved exposure to PCBs. In order to increase the likelihood that future subjects will be drawn from a sub-population of exposed workers, we have decided to limit subject recruitment to those individuals whose job codes indicate past exposure to PCBs. This approach, although different from that described in the initial application, will allow us to more adequately

address the question of whether high level exposure to PCBs alters behavior and brain dopamine function.

### **Progress in Fiscal Year 2004**

The following narrative provides descriptions of the progress we have made in the third year of the project—a period in which we have been actively engaged in data collection.

#### **We Have Succeeded Our Goal for Recruiting and Testing Subjects in 2004**

In the past year we successfully recruited and tested sixty-seven subjects in Albany, NY. As of 23 December 2004 we have tested a total of 129 subjects with ten additional subjects still scheduled, and are thus on schedule (Table I). See also Appendix 2 for a summary of the demographics for the tracing and screening activity to date. The tests conducted in Albany include: (i) administering a residential, occupational, dietary and medical history interview; (ii) completing neurological and neuropsychological assessments; (iii) measuring bone lead concentrations and (iv) collecting blood for measurement of serum thyroid hormone and PCB concentrations.

**TABLE I: Albany, NY Testing, Potential Subjects as of 24 Dec '04**  
n=297 (22 still in recruitment)

<b>GENDER</b>	<b>YES: 139</b>		<b>NO: 136</b>	
	<b>129 Complete and 10 Scheduled</b>			
Male	94	67.63%	74	54.41%
Female	45	32.37%	62	45.59%

<b>AGE</b>				
50s	54	38.85%	49	36.03%
60s	43	30.94%	30	22.06%
70s	34	24.46%	40	29.41%
80-90s	8	5.76%	17	12.50%

At completion of testing in Albany, subjects were asked if they wished to participate in the SPECT  $\beta$ -CIT imaging portion of the study carried out by Dr. Marek's group at the Institute for Neurodegenerative Disorders in New Haven, CT. Despite the fact that these procedures required a two day stay in New Haven and the injection of a radio-labeled tracer, we have met our goal of testing 24 subjects per year. These data are presented in Table II.

During the past year we completed testing subjects who had participated in earlier studies conducted by investigators from the Mt. Sinai School of Medicine in the late 1970's and early 1980's (*i.e.* those individuals with archived sera). Those individuals are important because we have access to their archived serum, and comparisons of current and archived serum PCB concentrations, will allow us to 'fine-tune' the algorithms needed to estimate historic serum PCB concentrations for the subjects for whom we do not have archived sera. Summary data for those subjects are presented in Appendix 3.

**TABLE II: New Haven, CT Testing, Potential Subjects as of 24 Dec '04**  
Subjects n=129 (35 still in recruitment)

		<b>YES: 48</b>			
		<b>39 Complete and</b>			
		<b>9 Scheduled</b>		<b>NO: 46</b>	
<b>GENDER</b>					
Male	34	70.83%	31	67.39%	
Female	14	29.17%	15	32.61%	
<b>AGE</b>					
50s	20	41.67%	11	23.91%	
60s	18	37.50%	11	23.91%	
70s	9	18.75%	19	41.30%	
80-90s	1	2.08%	5	10.87%	

We have also begun tracing, screening and testing of subjects who had not been previously tested by investigators at Mt. Sinai in the late 1970's and early 1980's (*i.e.*, non-archived individuals). Table III provides a description of those individuals who were traced, screened and recruited. Tracing refers to the procedures carried out to identify and locate individuals who potentially could take part in the study, while screening refers to the procedures carried out by staff at the Center for Environmental Health (a part of the New York State Department of Health) to determine if the individuals are medically eligible. If found eligible, the subjects' names were sent to the Study Coordinator, who contacted them to more completely describe the test protocols and schedule their visits to Albany.

**TABLE III: Subjects from Non-Archived Sera Cohort as of 24 Dec '04 (n=6488)**

<b>Tracing Results</b>		<b>Entered Tracing: 1400</b>	
Dead		413	29.50%
Out of Area		163	11.64%
Too Young		1	0.07%
Could not be Located		17	1.21%
<b>Eligible for Screening</b>		<b>512</b>	<b>36.57%</b>
Still in Tracing		294	21.00%
<b>Screening Results</b>		<b>Entered Screening: 512</b>	
Refused		87	16.89%
Medically Ineligible		154	30.08%
<b>Eligible for Recruitment</b>		<b>205</b>	<b>40.04%</b>
Still in Screening		66	12.89%
<b>Albany Testing:</b>		<b>Entered Recruitment: 205</b>	
<b>Recruitment Results</b>			
Participated		89	43.41%
Refused		94	45.85%
Still in Recruitment		22	10.73%
<b>New Haven Testing:</b>		<b>Entered Recruitment: 89</b>	
<b>Recruitment Results</b>			
Participated		23	25.84%
Refused		24	26.97%
Still in Recruitment		42	47.19%

Table IV provides a summary on those subjects who have either agreed or refused to participate in the study as of 24 December 2004.

**TABLE IV:** Summary of Subject Participation in Albany, NY and New Haven, CT Portions of the Study from Inception to 24 Dec '04

	Archived Sera Cohort (N=310)		Non-Archived Sera Cohort (N=6488)		All Subjects	
Albany Participation						
Yes, Participated	51	55%	78	38%	129	43%
Yes, Scheduled	0		10	5%	10	3%
To Be Contacted/Recruit Later	0		22	11%	22	7%
Refused	41	45%	95	46%	136	46%
TOTAL	92	100%	205	100%	297	100%
New Haven Participation						
Yes, Participated	23	45%	16	21%	39	30%
Yes, Scheduled	0		9	11%	9	7%
To Be Contacted/Recruit Later	6	12%	29	37%	35	27%
Refused	22	43%	24	31%	46	36%
TOTAL	51	100%	78	100%	129	100%

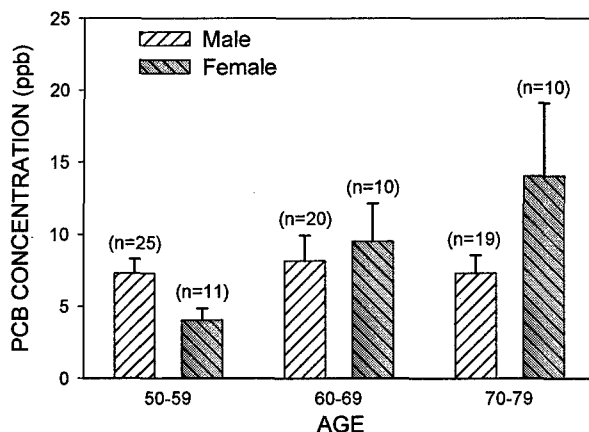


### Measurement of Serum PCB Concentrations

Dr. Mary Wolf, of the Mt. Sinai School of Medicine, is analyzing serum PCB concentrations from the former capacitor workers using glass capillary gas chromatographic techniques. Data includes not only congener specific determination of current serum PCB concentrations, obtained when the subjects travel to Albany, but also, for those individuals for whom we have archived sera, reanalysis using the same analytical procedures described in the grant application. The availability of both current and archived sera PCB levels, determined in the same laboratory using the same analytical techniques, allows us to more precisely estimate historic serum PCB levels for those individuals for whom we do not have archived sera.

The data presented below represents PCB analyses from 102 individuals broken down by age (decade) and gender. It is noteworthy that the serum PCB levels remain elevated (average PCB levels in non-occupationally-exposed individuals are approximately 2-3 ppb) more than twenty-five years after occupational exposure ceased. Although we chose to present only total PCB concentrations (a sum of lightly and heavily chlorinated congeners), subsequent analyses, particularly for levels of lightly chlorinated congeners that have short half-lives, will allow us to discriminate between occupational and more recent recreational and/or residential exposures.

**Figure 1.** Total Current Serum PCB Levels (mean  $\pm$  sem)



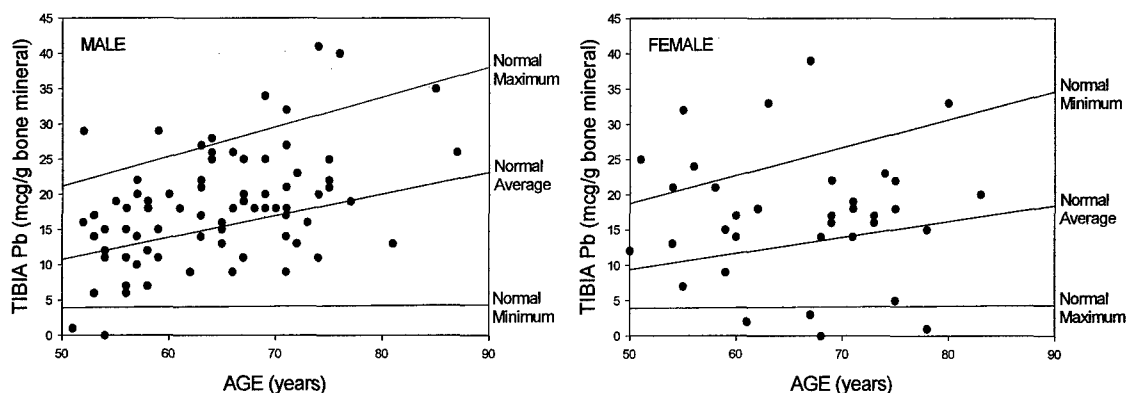
### Measurement of Bone Lead Concentrations by K-Shell X-Ray Fluorescence

Mount Sinai supervised the *in vivo* measurement of lead in bone in Albany and analyzed the raw data (in electronic form) generated with the bone lead measurement system. Mount Sinai personnel also continued to provide consultation on all aspects of the X-ray Fluorescence bone lead measurement system, including regular and *ad hoc* consultation, as required, on the quality of spectra acquired, the control and use of the measurement system and the reliability of the analytical results in order to provide both the most precise and the most reliable bone-lead data possible.

Mount Sinai personnel also supervised the Albany XRF operators in the daily operation of the XRF measurement system with regard to its maintenance, calibration, optimization and quality control protocol and have provided expertise on the optimization of the measurement system with regard to operational parameters of the spectroscopy electronics (*viz.* rise time, flat-top, *etc.*).

All calibration and human measurement XRF data have been electronically transmitted to the Mount Sinai XRF Laboratory for analysis. The analyses of the data received to date have been completed. Analyses of new data are being performed as they arrive. To date, sixty study participants have had their bone lead measured and analyzed. These bone lead data are presented below.

Figure 2. Tibia Lead (Pb) Concentrations by Age and Gender



The range of values for 'maximum' and 'minimum' are based on data from 13-16 studies of XRF measurement of bone lead concentrations obtained from non-occupationally-exposed men and women (Roy *et al.*, *Appl. Radiat. Isotopes*, 48, 391-6, 1997; Gamblin *et al.*, *Appl. Radiat. Isotopes*, 45, 1035-8, 1994) and are presented here to provide a framework in which to begin to interpret the concentrations of bone lead we have determined in the former capacitor workers.

### Investigators Meetings

In order to facilitate communication between these individuals who are located at the different institutions in Albany, we have met five times during the past year (March 9<sup>th</sup>, May 4<sup>th</sup>, June 4<sup>th</sup>, September 21<sup>st</sup> and December 7<sup>th</sup>). These meetings have proven to be extremely useful and allow us to avoid many of the pitfalls that might otherwise occur in the conduct of this complicated multi-institutional epidemiological study. Topics discussed included how to best report results to subjects' physicians if abnormal neurological and neuropsychological deficits are seen; issues of confidentiality and database development for reporting results for statistical analyses.

In June of last year a meeting was held in Albany that included all investigators from Albany and New Haven, as well as the epidemiology consultants, to present data that had been collected up to that time and discuss issues related to changing the procedures for identifying and testing future subjects.

### KEY RESEARCH ACCOMPLISHMENTS

As in all epidemiological studies, presentation of interim results prior to the collection of the entire data set and the accompanying statistical analyses to control for potential confounders is at best misleading and at worse may result in conclusions that are fallacious. Hence, the key research accomplishments are those described in the above sections.

### REPORTABLE OUTCOMES

Two abstracts that included data from this study were presented during the past year at scientific conferences. The first, entitled 'Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function' was presented in February 2004 at the Twenty-First International Neurotoxicology Conference in Honolulu, HI and the second, entitled 'PCBs, Dopamine and Cell-Death - Relevance to Human Exposure' was presented in September 2004 at the Superfund Basic Research Program Conference 'Persistent Contaminants: New Priorities, New Concerns' in Bear Mountain, NY (see Appendix 4).

### CONCLUSIONS

For the second year we have met our goal for recruiting and testing subjects, both in Albany, NY and in New Haven, CT. We are proud of this progress since many of our subjects are elderly (median age = 65 years) and must travel considerable distances to undergo testing at these two sites.

We are at the mid-point in the testing of subjects (to date we have tested 129 subjects; our goal is to test 248 subjects) and can now begin to carefully review the data to determine initial trends. For example, a review of the job histories of the most recently recruited subjects indicates a need to move from random selection of subjects to a recruitment procedure that emphasizes selection of the more heavily exposed subjects. We have begun this new selection process and will continue to do so for the remaining tenure of the grant.

We have shown that current serum PCB levels are significantly elevated in former capacitor workers compared to literature values for non-occupationally exposed individuals. These findings demonstrate, given the many years since occupational exposure ceased, the extraordinarily high levels of PCBs to which these workers had been exposed.

Finally, we will begin determining whether occupational exposure has altered thyroid hormone function in these workers and use that information to statistically determine the contributions of endocrine disruption in addition to those hypothesized to occur following reductions in central dopamine function.

### APPENDICES

**Appendix 1:** Curriculum Vita for Dr. Donald S. Higgins, Jr.

**Appendix 2:** Demographic Outcomes for Tracing and Screening Activity to Date.

**Appendix 3:** Summary of Participation for the Archived Sera Cohort.

**Appendix 4:** Abstracts from the International Neurotoxicology Conference, Honolulu, HI, February 2004 and the Superfund Basic Research Program Conference, Bear Mountain, NY, September 2004.

**APPENDIX 1**

Curriculum Vita for Dr. Donald S. Higgins, Jr.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Higgins, Donald S. Jr.</b>		POSITION TITLE <b>Associate Professor</b>	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Illinois Wesleyan University, Bloomington, IL	B.A.	1982	Biology /Chemistry
SUNY at Stony Brook, Stony Brook, NY	M.D.	1987	Medicine
The University of Michigan, Ann Arbor, MI	Intern	1988	Internal Medicine
The University of Michigan, Ann Arbor, MI	Fellow	1989	Neuroscience
The University of Michigan, Ann Arbor, MI	Resident	1992	Neurology
The University of Rochester, Rochester, NY	Fellow	1994	Movement Disorders

**A. Positions and Honors****EMPLOYMENT**

1994-1995 Senior Instructor, Department of Neurology, The University of Rochester  
 1995-2000 Assistant Professor, Department of Neurology, The Ohio State University  
 1998-2000 Assistant Professor, Department of Neuroscience, The Ohio State University  
 2000- Associate Professor, Department of Neurology, Albany Medical College  
 2000- Associate Professor, Center for Neuropharmacology and Neuroscience, Albany Medical College

**HONORS**

1983 Research Fellowship, Parkinson Disease Foundation, Columbia University  
 1988-1989 National Research Service Award (NS07222), The University of Michigan  
 1992 Notter Neuroscience Research Award, The University of Rochester  
 1992-1994 National Research Service Award (AG00107), The University of Rochester  
 1993 Travel Fellowship, American Neurological Association  
 2002 Distinguished Leader Award, Central Ohio Chapter, Huntington Disease Society of America

**SERVICE**

1997- Member, Editorial Board, Hospital Physician  
 1998 Clinical Sciences Special Emphasis Panel (ZRG1 SSS-G-05), Center for Scientific Review (CSR)  
 2000-2002 Member, Human Subjects Committee, Albany Medical College  
 2001 Member, Nominating Committee, Huntington Study Group  
 2000- Member, Grants Review Subcommittee, Huntington's Disease Society of America  
 2004- Temporary Member, Behavioral Medicine, Interventions and Outcomes Study Section, CSR  
 2004- Member, Center Program and Education Advisory Committee, HDSA  
 2004- Member, Clinical Protocol Working Group, Gene Therapy in Parkinson Disease

**B. Selected peer-review publications (in chronological order)**

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**C. Research Support**

**ACTIVE**

1 R01 NS40767-A01 (Shoulson – P.I.) 07/01/2002-06/30/2007

NIH; NHGRI, NINDS

Prospective Huntington At Risk Observational Study (PHAROS)

An observational study to prospectively determine, in a double-blinded controlled fashion, the rate of illness onset (phenoconversion) in individuals who are at immediate risk for inheriting the HD gene and who are unaware and wish to remain unaware of their HD gene status.

Role: Site Investigator

(Marshall – P.I.) 04/01/2003-03/31/2005

Prestwick Pharmaceuticals, Inc.

Tetrabenazine in Huntington's Disease (TETRA-HD)

A multicenter, placebo-controlled, safety, tolerability, dose-finding, and efficacy trial of tetrabenazine, an inhibitor of the vesicular monoamine transporter type 2 gene (VMAT2), in ambulatory HD patients.

Role: Site Investigator

(Higgins – P.I.) 07/01/2003 - 06/30/2005

Community Foundation for the Capital Region

Incorporation of Rehabilitation and Social Work into a Multidisciplinary Clinic for Huntington Disease

Prospective assessment of physical therapy, occupational therapy and social work services in Huntington disease.

Role: Principal Investigator

(Higgins – P.I.) 03/01/2004 – 06/30/2005

Pfizer Pharmaceuticals

Double-Blind, Placebo-Controlled Evaluation of Donepezil in the Management of Tourette Syndrome

Examination of cholinesterase inhibition as tic suppressant.

Role: Principal Investigator

(Higgins – P.I.) 03/01/2005 – 09/30/2006

Janssen Pharmaceuticals

Pilot Examination of Galantamine in the Management of Tic Disorders

Examination of cholinesterase inhibitor as therapy for tics.

Role: Principal Investigator

**OVERLAP**

There is no scientific overlap



## **APPENDIX 2**

### **Demographic Outcomes for Tracing and Screening Activity to Date**

# 2005 Progress Report

GROUP 1: Potential Subjects with Archived Sera		GROUP 2: Potential Subjects without Archived Sera	
Traced to Date: 310		Traced to Date: 1106	
n	%	n	%

## DEMOGRAPHICS: OVERVIEW

### Sex

Female	146	47.10%	446	40.33%
Male	164	52.90%	660	59.67%

### Agegroup

40s	0	0.00%	1	0.09%
50s	53	17.10%	261	23.60%
60s	55	17.74%	203	18.35%
70s	92	29.68%	270	24.41%
80s+	110	35.48%	370	33.45%
Unknown	0	0.00%	1	0.09%

## DEMOGRAPHICS: BY TRACING OUTCOME

### Sex

Sex	Eligible for Screening (n=192)		Eligible for Screening (n=512)	
Female	89	46.35%	220	42.97%
Male	103	53.65%	292	57.03%

### Not Eligible for Screening (n=118)

Female	57	48.31%	226	38.05%
Male	61	51.69%	368	61.95%

### Agegroup

Agegroup	Eligible for Screening (n=192)		Eligible for Screening (n=512)	
40s	0	0.00%	0	0.00%
50s	45	23.44%	182	35.55%
60s	41	21.35%	130	25.39%
70s	61	31.77%	133	25.98%
80s+	45	23.44%	67	13.09%
Unknown	0	0.00%	0	0.00%

### Not Eligible for Screening (n=118)

40s	0	0.00%	1	0.17%
50s	8	6.78%	79	13.30%
60s	14	11.86%	73	12.29%
70s	31	26.27%	137	23.06%
80s+	65	55.08%	303	51.01%
Unknown	0	0.00%	1	0.17%

# 2005 Progress Report

GROUP 1: Potential Subjects with Archived Sera		GROUP 2: Potential Subjects without Archived Sera	
Traced to Date: 310		Traced to Date: 1106	
n	%	n	%

## DEMOGRAPHICS: BY SCREENING OUTCOME

Sex	Refused (n=40)		Refused (n=87)	
	Female	26 65.00%	41 47.13%	
	Male	14 35.00%	46 52.87%	
	Medically Ineligible (n=60)		Medically Ineligible (n=154)	
	Female	27 45.00%	80 51.95%	
	Male	33 55.00%	74 48.05%	
	Passed to Recruitment (n=92)		Passed to Recruitment (n=205)	
	Female	36 39.13%	78 38.05%	
	Male	56 60.87%	127 61.95%	
Agegroup	Refused (n=40)		Refused (n=87)	
	40s	0 0.00%	0 0.00%	
	50s	6 15.00%	30 34.48%	
	60s	7 17.50%	19 21.84%	
	70s	12 30.00%	23 26.44%	
	80s+	15 37.50%	15 17.24%	
	Medically Ineligible (n=60)		Medically Ineligible (n=154)	
	40s	0 0.00%	0 0.00%	
	50s	12 20.00%	42 27.27%	
	60s	13 21.67%	42 27.27%	
	70s	18 30.00%	41 26.62%	
	80s+	17 28.33%	29 18.83%	
	Passed to Recruitment (n=92)		Passed to Recruitment (n=205)	
	40s	0 0.00%	0 0.00%	
	50s	27 29.35%	77 37.56%	
	60s	21 22.83%	58 28.29%	
	70s	31 33.70%	50 24.39%	
	80s+	13 14.13%	20 9.76%	

All results updated 12/24/04.

### **APPENDIX 3**

#### **Summary of Participation for the Archived Sera Cohort**

**Participation Results from Archived Sera Cohort as of 24 Dec '04  
(n=310)**

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**Tracing Results**

Dead
Out of Area
Too Young
Could not be Located
<b>Eligible for Screening</b>
Still in Tracing

**Entered  
Tracing: 310**

97	31.29%
21	6.77%
0	0%
0	0%
<b>192</b>	<b>61.94%</b>
0	0%

**Screening Results**

Refused
Medically Ineligible
<b>Eligible for Recruitment</b>
Still in Screening

**Entered  
Screening: 192**

40	20.83%
60	31.25%
<b>92</b>	<b>47.92%</b>
0	0%

**Albany Testing:  
Recruitment Results**

Participated
Refused
Still in Recruitment

**Entered  
Recruitment: 92**

51	55.43%
41	44.57%
0	0%

**New Haven Testing:  
Recruitment Results**

Participated
Refused
Still in Recruitment

**Entered  
Recruitment: 51**

23	45.10%
22	43.14%
6	11.76%

#### **APPENDIX 4**

Abstracts from  
International Neurotoxicology Conference,  
Honolulu, HI, February 2004 and  
Superfund Basic Research Program Conference,  
Bear Mountain, NY, September 2004

## INTERNATIONAL NEUROTOXICOLOGY CONFERENCE 2004

Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function. RF Seegal<sup>1</sup>, KL Marek<sup>2</sup>, SA Factor<sup>3</sup>, RJ McCaffrey<sup>4</sup>, RF Haase<sup>4</sup> and AG Kanthasamy<sup>5</sup>. <sup>1</sup>Wadsworth Center, New York State Dept. of Health, Albany, NY; <sup>2</sup>Institute for Neurodegenerative Disorders, New Haven, CT; <sup>3</sup>Albany Medical Center, Albany, NY; <sup>4</sup>University at Albany, Albany, NY and <sup>5</sup>Iowa State University, Ames, IA.

PCBs reduce dopamine (DA) concentrations and the number of tyrosine hydroxylase positive neurons in the substantia nigra of adult rodents and nonhuman primates (NHPs). This loss of function may involve inhibition of monoamine transporters, including the vesicular monoamine transporter, consequent metabolism of cytosolic DA, induction of oxidative stress and apoptosis. Indeed, in a midbrain DA cell line (N27), PCBs induce oxidative stress to a greater extent than MPP+. In order to determine whether these findings induce similar changes in humans we are studying the behavioral and structural consequences of prior long term high level exposure to PCBs in a cohort of former workers. This epidemiological study will determine if prior PCB exposure alters DA mediated behaviors, including motor function, memory and neurological function and the number of DA terminals in the basal ganglia, determined using  $\beta$ -CIT SPECT imaging. This epidemiological study will allow us to begin to determine whether laboratory data demonstrating the neurotoxicity of PCBs can be extrapolated to humans and may provide additional evidence concerning the role of environmental neurotoxins in the etiology of parkinsonism (*e.g.*, dioxins and furans) on human DA function, including Parkinson's disease. Supported by grants from the US Army Medical Research and Materiel Command, NIEHS and EPA to RFS, and NIH to AGK.

## **SUPERFUND BASIC RESEARCH PROGRAM CONFERENCE 2004**

PCBs, Dopamine and Cell Death - Relevance to Human Exposures? R.F. Seegal<sup>1,2</sup>, A. Dreiem<sup>1</sup>, G. Lyng<sup>2</sup> and AG Kanthasamy<sup>3</sup>. <sup>1</sup>Wadsworth Center, NYSDOH; <sup>2</sup>School of Public Health, University at Albany, Albany, NY and <sup>3</sup>Iowa State University, Ames, IA.

Although many epidemiological studies suggest an association between developmental exposure to polychlorinated biphenyls (PCBs) and behavioral deficits in infants and children, recent studies carried out in adults have also found an association between PCB exposure and behavioral change. Although the mechanisms for these deficits remain largely unknown, recent evidence from *in-vitro* laboratory studies of neurons in culture, as well as *in-vivo* studies of adult non-human primates (NHPs), demonstrate that PCBs alter dopamine (DA) function and neuronal viability in the mature central nervous system and may thus contribute to the aforementioned changes in behavior.

PCBs are potent inhibitors of monoamine transporters, including the vesicular monoamine transporter (VMAT) responsible for the sequestration of cytosolic DA. In turn, elevations in free cytosolic DA, due to VMAT inhibition, lead to formation of hydrogen peroxide and reactive quinones and semi-quinones. PCBs also induce reactive oxygen species and apoptotic neuronal death in a rat mid-brain dopaminergic cell line that can be inhibited by superoxide dismutase mimetics and caspase inhibitors. These *in-vitro* mechanisms may aid in explaining the long-term reductions in striatal DA concentrations and the number of DA-containing neurons seen in the basal ganglia of NHPs following long-term exposure to PCBs.

In order to determine whether similar changes occur in humans we are studying the neurological consequences of prior long-term high level exposure to PCBs in a cohort of former workers. This epidemiological study will determine if: (i) prior exposure alters DA mediated behaviors, including motor function, memory and neurological function, and the number of DA terminals in the basal ganglia using  $\beta$ -CIT SPECT imaging and (ii) environmental contaminants, including PCBs, are etiologic factors in parkinsonism.

Supported by grants from the US Army Medical Research and Materiel Command, NIH and EPA to RFS and NIH to AGK.